REMARKS

The foregoing amendments and the following remarks are submitted in response to the communication dated February 6, 2008.

Status of the Claims

Claims 1, 3-7, and 28 are now pending in the application as above amended. Claims 2, 85-87, 104, 107-109, 116, 117, 123, 130, 131, and 138-148 have been canceled. Claims 1 and 28 have been amended in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims can be found generally through Applicants' specification.

Sequence Rule Compliance

The Examiner asserts that the Application fails to comply with the requirements of 37 C.F.R. 1.821 through 1.825 because Figures 4A and 5A contain nucleic acid sequences that are not preceded by appropriate SEQ ID NOs. The Examiner requests that the figures or the description of the drawings be amended accordingly. Applicants submit herewith a revised substitute Sequence Listing and replacement Figures for 4A and 5A. In particular, we note that the substitute Sequence Listing has been modified, and now includes SEQ ID NOs: 34-40, which correspond to the sequences set out in Figures 4A and 5A. The sequence correspondence is annotated to provide reference to the appropriate SEQ ID NOs in the enclosed replacement Figures. The sequence listing modifications are as follows:

- Subheading <212> for SEQ ID NOs: 1 to 4, 7 to 10, 12 to 14, 18 to 29, 32 and 33 has been amended to read "RNA" since these sequences refer to RNA sequences;

- SEQ ID NO: 34 corresponds to the sequence of oligonucleotide X-M4A1W published in Figure 4A and is actually a combination of SEQ ID NO: 12 and SEQ ID NO: 10;

- SEQ ID NO: 35 corresponds to the sequence of oligonucleotide X-M4A1M published in Figure 4A and is actually a combination of SEQ ID NO: 13 and SEQ ID NO: 10;

- SEQ ID NO: 36 corresponds to the sequence of oligonucleotide C5-M4A1 published in Figure 5A and is actually a combination of SEQ ID NO: 5 and SEQ ID NO: 4;

- SEQ ID NO: 37 corresponds to the sequence of oligonucleotide C5-M4CT published in Figure 5A and is actually a combination of SEQ ID NO: 6 and SEQ ID NO: 4;

- SEQ ID NO: 38 corresponds to the sequence of oligonucleotide C5-M4A1W published in Figure 5A and is actually a combination of SEQ ID NO: 7 and SEQ ID NO: 4;

- SEQ ID NO: 39 corresponds to the sequence of oligonucleotide C5-M4A1M published in Figure 5A and is actually a combination of SEQ ID NO: 8 and SEQ ID NO: 4;

- SEQ ID NO: 40 corresponds to the sequence of oligonucleotide C5-M26A1 published in Figure 5A and is actually a combination of SEQ ID NO: 5 and SEQ ID NO: 3.

Applicant submits that all the sequences included on the substitute Sequence Listing were included in the Application as filed. Applicant asserts that the enclosed substitute Sequence Listing and replacement figures do not include new matter. Applicant requests entry and inclusion of the substitute Sequence Listing in the instant file wrapper and specification and request acceptance of the Application as fully compliant with the requirements of 37 C.F.R. 1.821 through 1.825.

Priority

The Examiner asserts that Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing under 35 U.S.C. 119(e). In particular, the Examiner argues that the priority Application No. 60/402,765 fails to provide adequate support for the claimed SEQ ID NO: 12, and fails to provide adequate enablement for the claimed subject matter of claim 7. Applicant respectfully submits that the subject matter of claim 7 is supported by the priority application. To this end, the Examiner is referred to the paragraph bridging page 19 and 20 as well as Example 4, particularly including the paragraph bridging pages 48 and 49 of the priority application 60/402,765. Support for SEQ ID NO: 12 is found, including in Table 1 of the priority application 60/402,765.

Specification

The disclosure is objected to because of the sequence rule-noncompliant subject matter noted above, and further as containing erroneous or inconsistent information on page 19. Applicants have above addressed the sequence compliance objection and respectfully request the rejection of the specification based on sequence non-compliance be withdrawn in view of the above and enclosed Figures and Sequence Listing. With regard to the objection based on erroneous information on page 19, the Examiner argues that the description of Figure 5A recites "in vivo" when in fact the data/results presented in Figure 5A were obtained by in vitro experiments. Applicants have above amended the specification at page 19 and the description of Figure 5A-5B to state "in cultured cells". Applicants submit that the Examiner's objection has been fully and satisfactorily addressed and should properly be withdrawn.

Claim Objections

Claim 28 is objected to for containing non-elected SEQ ID NOs. Claim 28 has been above amended to remove the non-elected SEQ ID NOs and to properly refer to the elected SEQ ID NO. Applicants request this objection be withdrawn.

Particularity and Distinctiveness of the Claims

The Examiner has rejected claims 2 and 28 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention.

The Examiner rejects Claim 2 in the language "effected". Claim 2 has been cancelled above, thereby rendering the objection moot.

Claim 28 is objected to in the language "oligonucleotide moiety", the Examiner arguing that antecedent basis for this language is insufficient in claim 1. The term "moiety" has been removed from claim 28. Applicant asserts that claim 28 is definite and clear.

Applicant requests that the Examiner withdraw the indefiniteness rejections.

The Specification Fully Enables the Claimed Invention

The Examiner has rejected claims1-7 and 28 under 35 U.S.C. 112, first paragraph, because the Examiner asserts that the specification, while enabling for a method of modulating splicing site selection in a cell *in vitro*, does not reasonably provide enablement for the method performed *in vivo* or in a cell that is in a patient. The Examiner argues that the specification does not enable any person skilled in the art to which it pertains, or with which it is most connected, to make and use the invention commensurate in scope with these claims.

Applicant submits that the specification does provide sufficient and appropriate guidance for the claimed subject matter. The data shown in the specification and Examples includes *in vitro* experiments in cell extracts and nuclear extracts, and cellular experiments in cultured cells and in various cell lines. Applicant adds that the data provided for *in vitro* and cell culture techniques found in the present patent application correlates to the *in vivo* method. To this end, the Examiner is referred to the Roberts et al. (2006), Sazani et al. (2002) and Suwanmanee et al. (2002) enclosed documents that confirm that the antisense technology can be successfully applied *in vivo*.

Further, as indicated in section 2164.02 of the MPEP:

> *"The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate."* [emphasis added]

Applicant does submit that the present application discloses working examples of the technology that correlates with the claimed subject matter. Reconsideration is respectfully requested. In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph, may properly be withdrawn.

Claim Rejections – 35 USC § 102

Claims 1-6 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by Newman et al (US 2002/0068321). Newman et al is cited as teaching a method of modulating RNA splicing and RNA splice site selection in cells *in vitro* by using a polynucleotide that is complementary to hnRNP A1 to block the activity of hnRNP A1, which promotes alternative splicing and splice site selection.

Applicant respectfully submits that Newman does not teach all the limitations of the claimed subject matter. Newman fails to disclose that the oligonucleotides to be used must (i) be complementary to a specific region upstream of a splice site in a target pre-mRNA molecule; and (ii) contain an extension containing a protein binding site sequence element for binding a protein moiety. Therefore, Newman cannot anticipate the presently claimed subject matter.

In his patent application, Newman suggests two ways of modulating splicing:

1) The first option consists in designing oligonucleotides targeted to specifically bind to a pre-mRNA sequence which is known to bind to a splicing factor (e.g. a nucleotide binding protein/RNA binding protein/RNA alternative splicing regulatory protein/nhRNP/hnRNP A1). As such, the oligonucleotide(s) inhibit the binding of the splicing factor to the pre-mRNA and thus modulate splicing. This option is set forth in paragraph [0375] of Newman.

2) The second option consists in designing oligonucleotides targeted to specifically bind to the splicing factor itself. This option is set forth in paragraphs [0364] to [0374] of Newman. In this option, the splice factor is actually titered out of the reaction and thus splicing is modulated.

In the present application, the oligonucleotides of the claimed method (i) bind to a nucleic acid sequence that is complementary to a specific region upstream of said splice site in said target pre-mRNA molecule and (ii) comprise an extension containing a protein binding site sequence element for binding a protein moiety. Newman fails to indicate that the

oligonucleotides used in the methods he describes must have these two properties, or to even suggest this.

In view of the foregoing remarks, Applicant requests that the Examiner's rejection under 35 U.S.C. 102(a) and (e) be withdrawn.

Claim Rejections – 35 U.S.C. § 103

The Examiner has rejected claims 1-6 and 28 under 35 U.S.C. 103(a) as being unpatentable over Newman et al (US 2002/0068321) as applied to claims 1-6 above, further in view of Taylor et al (Nature Biotechnology (1999) 17:1097-1100, applicant's citation).

Applicant respectfully submits that Newman does not teach or suggest the claimed subject matter, and further, a person skilled in the art would not be led or motivated to adapt the teachings of Newman to obtain the claimed subject matter. As indicated above, Newman does not teach that the oligonucleotides need to (i) bind to a nucleic acid sequence that is complementary to a specific region upstream of said splice site in said target pre-mRNA molecule and (ii) comprise an extension containing a protein binding site sequence element for binding a protein moiety.

Taylor et al is cited as teaching a method of modulating Bcl-x pre-mRNA splicing by antisense oligonucleotides in cultured human cells *in vitro*, wherein the modulating step produces increased Bcl-xS expression while reducing the production of Bcl-xL. Bcl-xL and Bcl-xS are produced by alternative splicing of the Bcl-x pre-mRNA. Taylor teaches modulating the Bcl-x pre-mRNA splice site selection by inhibiting the use of the 5' splice site in exon 2 of the Bcl-x RNA by antisense oligonucleotides hybridizing upstream of the Bcl-xL splice donor site. Taylor does not teach or suggest Applicant's method. Taylor does not teach or suggest oligonucleotides that (i) bind to a nucleic acid sequence that is complementary to a specific region upstream of said splice site in said target pre-mRNA molecule and (ii) comprise an extension containing a protein binding site sequence element for binding a protein moiety. The combination of Newman and Taylor does not make obvious Applicant's claimed invention.

Applicant respectfully submits that oligonucleotides that (i) bind to a nucleic acid sequence that is complementary to a specific region upstream of said splice site in said target pre-mRNA molecule and (ii) comprise an extension containing a protein binding site sequence element for covalently binding a protein moiety are more specific than the oligonucleotides described in Newman (which lack at least one of the above-mentioned limitations). To this end, the Examiner is referred to the enclosed declaration by inventor CHABOT which compares the efficiency of different oligonucleotides on the modulation of splicing. The data presented in the declaration clearly indicate that oligonucleotides that (i) bind to a nucleic acid sequence that is complementary to a specific region upstream of said splice site in said target pre-mRNA molecule and (ii) comprise an extension containing a protein binding site sequence element for binding a protein moiety (such as the TOSS oligonucleotide) modulate splicing more efficiently than the oligonucleotide described in Newman (such as the As or the ASCasp8-4 oligonucleotides) or the control oligonucleotide (such as the TOSS AllStar oligonucleotide).

Applicant further submits that what Newman teaches and suggests is the inhibition of interaction between the pre-mRNA and the protein for modulating splicing. Newman teaches to either block the protein binding site on the pre-mRNA (by using an antisense oligonucleotide) or titer off the protein itself (by using an oligonucleotide that binds to the protein). On the other hand, the present patent application teaches that the oligonucleotide must bring into proximity the target pre-mRNA and the protein, which is distinct and unobvious from the teachings of Newman, even in view of Taylor et al.

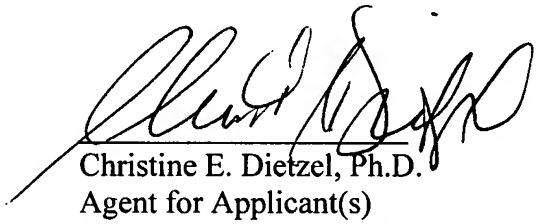
In light of the above, Applicant respectfully submits that the claims on file are not obvious in light of Newman in view of Taylor, and respectfully requests reconsideration.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

KLAUBER & JACKSON, LLC



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